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HISTORICAL ARCHIVES

Substitution of renal function through skin catharsis: Evidence from the classical period to the Middle Ages

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Substitution of renal function through skin catharsis: Evidence from the classical period to the Middle Ages. The skin's cleansing capacity has been known for centuries and has been used therapeutically and extensively for a great number of diseases. We studied the historical evolution of the methods used for catharsis through the skin, particularly for those in renal failure, by reviewing most of the existing ancient Greek and Byzantine codices dealing with the skin's cleansing capacity. From the fragments cited in this article, it is evident that the ancient medical writers were well aware of the mechanism of perspiration, and through this process the excretion of several body toxins, they knew about renal failure as well as the influence of environmental temperature on blood purification via the skin. To validate their views, we reviewed the seasonal variation of the average values for blood urea, creatinine, and electrolytes for 161 regular dialysis treatment (RDT) patients in four dialysis units in southern Greece. The estimations were carried out during the winter/summer 1997, 1998, and 1999 terms and included three winter months and three summer months. We traced an unexpectedly large number of references in the ancient and medieval Greek medical literature concerning detoxification through the skin, mainly regarding patients in renal failure. This seasonal variation hypothesis is supported by the results of our retrospective study: there was a difference of 16 mg/dL in the average blood urea (mean winter urea 182 mg/dL, mean summer urea 166 mg/dL). We suggest that the ancients had a vivid idea about the substitution of renal function by the skin's cleansing ability in renal failure. The previously mentioned phenomenon may be due to the elimination of blood urea through excessive perspiration. Our clinical results seem to verify their notions, and hence, the skin (like the peritoneum) may be considered a natural membrane for dialysis. We were unable to trace a similar report in the literature on the seasonal fluctuation of blood urea in dialysis patients.

For the past five years we have been interested in the study of the cathartic ability of various biological membranes [1]. More recently, we investigated in some detail the historical development of the use of the skin as an alternative route for catharsis in edematous and/or uremic humans. The reviewed literature was vast. Hence, this article presents only the first portion, extending from the classical period to the end of the Middle Ages. In a forthcoming report, we will present our findings from the historical literature from the Middle Ages up to the present time.

Being enthralled by the ancients' suggestion that the skin increases its cleaning ability in cases with renal failure, we attempted to test its validity on clinical grounds. Our findings show a significant decrease of the regular dialysis treatment (RDT) patients' blood urea during the summer months. Although the idea of seasonal variation of biochemical and other parameters of humans and animals has not been ignored by the scientific community [2–4], we were unable to trace any similar report in the literature as far the mechanism that could explain this variation. We suggest that this decrease in our patients' blood urea occurs because of its elimination through increased perspiration during the warmer period of the year. If this hypothesis is correct, then the ancients' idea on the role of the skin as an alternative kidney is confirmed. It is interesting to note that the impact of the seasonal variations was very well known to the ancient Greeks as Hippocrates clearly stated in the following aphorism, "*From all the weather conditions of the year the healthier and less deadly ones are the droughty and the rainless compared to the wet and rainy*" [5].

Fourteen centuries later, Theophilus Protospatharius and Damascius commented on this aphorism and gave the following explanations:

"Theophilus: . . . *So, from all the seasons, as Hippocrates stated, the droughty are healthier and less deadly than the rainy ones. Because on the droughty seasons sweating eliminates the unwanted liquids, while on the rainy ones* (the liquids) *are collecting inside the body and rotten thus causing many problems.*" Damascius concurred, "*Because on the droughty seasons sweating eliminates the unwanted liquids, while on the rainy ones* (the liquids) *are collecting inside the body and rotten; except if one*

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eliminates them every day by exercising or bathing or some other practice" [6].

Methods

The historical materials of this research include practically all of the existing relevant Classical, Hellenistic, Roman, and Byzantine Greek codices, dating from the fifth century B.C. to the fifteenth century A.D. We read them in the various original dialects of the Greek language, and then translated them into English.

CLASSICAL AGE: EMBEDOCLES, HIPPOCRATES, ARISTOTLE (500 TO 300 B.C.)

Birth of physiology: The porosity of objects in nature

The original observations of the various natural phenomena, whether wrongly or properly interpreted, led to the gradual development of theories pertaining to the interpretation of human's physical mechanisms. The transfer of macrocosmic phenomena and their adaptation to the microcosm of humans and animals was the first step of this approach, and the observer had every reason to make this contrast. Menstruation, being adapted to the moon's periodical appearance and disappearance, naturally did not go unnoticed. The earth itself had been personified and thus became a living organism that got warm, cold, or dry or was able to perspire. An essential parameter that applied to these observations was the awareness that all geologic and biological phenomena resting on mass or energy exchange were grounded on the existence of porous bodies. An old reference is given by Empedocles in his description for the receptivity of the senses:

"*Every body is affected seeing that it is penetrated through a number of pores by that substance which ultimately exercises its active influence and, thus, we see and hear and feel along with the other feelings* (that exist). *Moreover, things become visible despite the fact that air and water as well as other transparent bodies intervene due to the reason that these intervening bodies have pores which by virtue of their smallness are invisible; nevertheless, they are dense and they are arranged in series connection, and most of the transparent objects have more pores*" [7]. An early reference of what centuries later will be termed an embryonic experimental proof of transcutaneous respiration is initially given, again by Empedocles, in his effort to explain the kinetics regarding the exchange of gases through the skin and combine it with the circulation of the blood. The idea was original in its conception:

"*Furthermore, all* (animals) *inhale and exhale in the following way. All animals have fleshy tubes that are void of blood and, in addition, these tubes are spread on the skin's surface. Onto the orifices of these tubes the body's uttermost surface has been cleaned through being furrowed with dense pores in such a way as to be able to contain the blood* (in the body)*; a clean passage however, should be opened up for the air by means of the cuts and through the pores. Owing to this fact, when the thin blood rushes to an opposite direction in relation to these pores, the air dashes in them as an unrestrainable wave. When the air springs again through* (the center of the body) *to the surface, then the air is exhaled outwards. A similar event occurs when a young girl plays with a clepsydra made of glistening copper. When she supports the opening of the bottle's neck with her lovely hand and sinks the clepsydra into the silver-colored water, the air can no more enter the vessel whereas the volume of air from within obstructs it as it falls onto the little pores until the girl* (having withdrawn her hands) *provides a free passage so that a dense stream of air comes out. Now then when the air has vacated the interior of the clepsydra, a proportional quantity of water comes into. The same occurs when the water has occupied the deep interior of the vessel, and through the human skin* (that is, with the hand), *the pore and the neck* (of the vessel) *as well as the outside air have been obstructed due to the fact that the air has been obsessed with the idea of penetrating into the vessel, holding the water at the neck's outlet, producing a deep sound, maintaining under its possession the edge of the neck, until the girl provides a way out by removing her hand. Then, after this and exactly in the opposite direction, compared to what occurred before, the air falls inside and a proportional quantity of water is withdrawn. The same occurs with the blood that is moving with vehemence through the body's parts. When it rushes inwards by returning backwards then the stream of air penetrates with swift undulation. When the blood rushes upwards from the body's depth, the air is exhaled outwards in equal proportion(s).*" [8].

The hydrological cycle regarding the earth as described by Aristotle was transferred to the human's body in order to explain human physiology. With food the human received the nutritional substances necessary for life. These substances were digested and classified into the useful ones that remained in the body and the useless ones that were eliminated. The final carrier of the food, the undigested elements of food as well as the remnants of digestion, was the blood. The blood should ultimately undergo catharsis. A healthy body realized this catharsis through the intestinal tube (that is, in the form of feces), through the lungs (a reference to a statement attributed to Aristogenes was given by Aristotle [9]), through the kidneys by urine production, and through the skin by perspiration. According to Aristotle, some animals had no bladder because the nature of their bodies was not as warm as of other animals, and as such did not need to consume water and did not have liquid excrements.

"*Therefore not all animals have a bladder, as it seems that nature decided to give* (a bladder) *only to those which*

have a lung swarming with blood which is reasonable for them. Because in these that have such an organ, this nature (the warm) *outweighs and are thirstier than the others and need not only dry food but more liquid and therefore their excretions are more than those their stomach can digest that have to be excreted. So there is a need for some organs to collect these excretions as well. So the ones* (animals) *that have such a lung also have a bladder, while from those that don't, others drink less because their lung is spongy, and others, whatever liquid they need, they consume as food and not as a liquid like the insects and the fish, and similarly the alate and the squamate and the lepidoids, because of the small quantity of liquid they consume and because they convert to such* (tissue) *the extra excretion, none of them has a bladder, except the turtle from the squamates*" [10].

Aristotle believed that "*the blood-swarming animals have a warm nature.*" The skin plays a significant role for the proper operation of the body, in that it constitutes a route for catharsis with regard to the substances that are to be eliminated. Aristotle, in his treatise titled *Meteorologics*, considered that there was a common reason for the creation of saline urine, of the even more saline respiration and of the salty sea: water passed through the soil, and the earth retained those elements that were useful, eliminating those that were salty and useless. Sweat was salty like seawater [11].

Moreover, Aristotle in his *Problems*, in the chapter titled *"On Perspiration"* questioned himself: "*Why is perspiration salty? Because, since it is provoked by movement or heat, anything considered as unfamiliar to the blood or the fleshes is eliminated from the food. And soon this* (alien substance) *is separated and discharged. And it is salty considering that the body consumes whatever is sweet and rejects a substance that is alien and indigestible. And the latter when is discharged from below is called urine whereas when it is eliminated through the skin is called perspiration. Both are saline for the same reason*" [12].

Aristotle's observations on perspiration seem to have derived from relevant observations made on natural phenomena as described in *Meteorologics* [13].

Further than the Earth's natural cathartic process, there was also the catharsis of the built or man-made environment. Hercules purified the Augea's barns by turning the Alpheus river's stream to run through them. The way that the rain fell and thus cleaned the city's roads offered ideas for the purification of the body. Both the earth and the city were cleaned by the falling rain and the running water. Humans and animals were cleaned by the water they drank and the liquids they discharged [14]. Aristotle correlated the city and the environment with the good health of the body [15]. This correlation was developed and refined by the Byzantines, as discussed later in this article.

Hippocratic pathophysiology

Hippocrates, the father of medicine, in his book, *On Sufferings*, referred to the cause of edemas and described them with exceptional detail: "*An edema is mostly caused when catharsis does not occur, as in the case of a long-standing disease*" . . . "*When an edema is attributed to the absence of catharsis, then the abdomen is filled with water and the legs up to the shins are swollen while the shoulders, the chest and the thighs languish*" [16].

According to Hippocrates, the humors and the fleshes were interchangeable both in health and in disease. The flesh could melt and become water and fill up the body's cavities. Hippocrates identified four forms of renal diseases. In his work *On the Inner Sufferings*, he described them as follows, "*Renal diseases are caused when the kidneys, having received the phlegm or choler or pus that is to be excreted, cannot eliminate them, resulting in its accumulation inside the kidneys and thus the appearance of the disease occurs.*" To put it another way, this mechanism, which was actually suggested by Hippocrates, was identified with the reduction of the cathartic ability of the kidneys [17].

Therapeutics through the skin

These conclusions of the views on pathophysiology also influenced the therapeutic approach to the issue. When the body malfunctioned and a therapeutic intervention was required, then catharsis was accomplished through either the intestinal tube with emetics, purgatives and enemas, or the skin. The most common method of catharsis through the skin was that of provoking perspiration. In ancient times, this was achieved with embrocations, cataplasms, sunbathing, and sand baths. A reference to the latter was not made by Aristotle nor does it exist in any written text of the period from 800 to 300 B.C. Later, however, Orivasios (fifth century A.D.) attributed such a reference to Herodotus (fifth century B.C.), and Antyllus (third century A.D.) did the same for Aetius (1st century A.D.). Nevertheless, the most widespread method was thermal baths and steam baths. In particular, "pyries" was a kind of a thermal bath that was accomplished by heating stones onto which water was thrown so that water vapors were produced, similar to modern saunas. The most significant reference to the use of thermal baths with regard to catharsis through the skin was given in Hippocrates' work, *On the Use of Water*:

"*Warm water is employed for sprinkling(s) and steam baths that affect the entire body or some part of it as well as for the softening of rough skin, the relaxation of the tensed skin and the contracted nerves, the ecchymosis of fleshes and the excretion of sweat.*" [18].

In *On Diet of Acute Diseases*, a work the authenticity of which was disputed by many, was written in the same period, and the author mentions, "*The defeat of all diseases*

is accomplished either orally or from the abdomen or by the bladder or by some other organ. The cure provided by perspiration is a common one for all (diseases)" [19].

In the same book the author writes, "*If we believe that we must make catharsis with the use of drugs, it is much safer to perform it from above* (that is, from the mouth with emetics) *with the use of hellebore. We should then abstain from the cathartic methods performed from below* (that is, diuretic drugs and enemas). *The best of all though is to provoke diuresis and perspiration and get the patient walking*" [20].

In his book *On Inner Sufferings*, Hippocrates referred to the treatment of all four categories of renal diseases. For all of them, apart from prescribing diuretics and cathartic drugs, the treatment included hot compresses, thermal baths, and steam baths. A few references to skin catharsis were also made by Aristotle. Cataplasms had cathartic ability as well: "*What is the efficiency of a cataplasm? It is to soothe and provoke perspiration and exhalation*" [21].

In general, however, there was a lack of enthusiasm on behalf of the ancient Greeks regarding the experimental proof of their theories. This can be attributed to their general repulsion for manual work as well as to their philosophical stance that urged them to try to prove ceaselessly the grand principles of cosmology, biology, and politics on the basis of a rather latent theology or dialectical extremes, rather than being occupied with detailed work. In their discussions, they were pioneers in their tendency to place arguments above authoritative views. Their energy, however, was spent on argumentation against rival theories, acting in favor of the correctness of their own, without taking particular care in proving scientifically, and in detail, their theses [22]. They always tried to describe the forest without having previously perceived entirely what is a tree. Thus, they were opposed to the modern tendency of many researchers to produce a flood of observations with no final unified result, in effect describing so many trees that in the end the general view of the forest is lost. Aristotle, in the fourth century B.C., consciously tried to turn the philosophers' interest to the common experiment, being, therefore, in contrast to the theory of Plato, his teacher.

LATE ANTIQUITY: ERASISTRATUS, ACHIGENES, GALEN, ARETEUS, RUFUS (300 B.C. TO 300 A.D.)

This section describes the views on catharsis during the classical age with the ideas of the poet and philosopher, Empedocles, and continue the corresponding description for later antiquity with other poets' views. During the first century A.D., Ovid, in his poem "*Metamorphoses*," described the ability of the humanized earth to absorb and re-excrete liquids when he told of the killing of Marsya and the shedding of tears for his death: "*The fertile earth got soaked, and soaked it caught the tears and drank them deep into her veins. Transforming them into water, she sent them back out again to the open air*" [23].

During the same period and in his poem "*On the Nature of Objects*" (50 B.C.), Lucretius presented a more altered version of the entire body's pores, which corresponds to our topic more fully: "*I will now try to remind* (you) *of how poriferous a body all things have, a fact which was also stated in my previous ode. Because, truly, although the fact that we realize this is important for many things, and at any event for those which I am going to straightforward speak, it is more than necessary to be certain that there is nothing more than* (the truth) *that a body is perforated by pores. One first such complex* (gives evidence for this): *in caves, the rocks above our heads discharge moisture and percolate muddy drippings. Likewise, sweat drips from our whole body*" [24]. It is very important to realize that during these early phases of scientific thought, the concept of the communication of the body with the environment through the skin and the application of the four elements theory was implicitly understood and interlaced with all scientific applications, not only medicine.

Birth of experimental physiology

An impressive outcome of the methodology as initially introduced by Aristotle was a reference found in the papyrus "*Anonymous Londiniensis*," probably written after the first half of the first century A.D. In it, a description of an experiment of Erasistratus of Cos (300 to 250 B.C.) was found:

"*. . . and Erasistratus performed the following experiment, he took an animal such as a hen or some other similar fowl and placed it into a caldron without providing it with food for quite some period of time. Then he weighed this fowl and its obvious excrements and he found them to be much less than the initial weight; thus he inferred that many discharges cannot be seen. This theory however, applies to man also. When men have drunk perfumes or have eaten garlic, this is made evident through their smell although is not otherwise sensible*" [25].

A logical conclusion from the previously mentioned text was to assume that insensible transpiration was not only known to ancient Greeks, but it was also experimentally proven by them with a more or less quantitative measurement [26].

Galen's natural and provoked skin catharsis

Galen's observations on physiology and on the function of various organs were unique. He identified the use of kidneys as a means of catharsis, which when they did not function properly, were substituted by other organs such as the gastrointestinal system and the skin. In particular, regarding the skin, he further developed

Empedocle's theory and claimed that the skin was full of pores resembling a sieve. He also maintained that under and onto the skin the arteries and the veins were anastomosed between them through minor pores (thus suggesting the function of the capillaries centuries before Harvey and Malpiggi). As a matter of fact, he concluded that aspiration and expiration were accomplished through the skin's pores [27]. Galen expanded the theory of the four humors that he derived from Hippocrates. According to Galen, sudden edemas were attributed to the inefficiency of the kidneys to eliminate fluids, and he very elegantly differentiated between the anuria caused from kidney or bladder dysfunction [28]. Galen knew very well the cathartic ability of the skin. He was aware of the fact that the generation of perspiration purified the body and that this occurred both for those who suffer of a disease as well as for healthy people, since he wrote later: "*Sweating then purifies the body. Indeed, similar to this* (that is, perspiration) *is that which is produced by low-effort exercise, baths and the summer heat.*"

It is exactly on the effect of the summer heat over the RDT patients' blood urea that the last paragraphs are based.

Areteus' opinions on the skin's natural alternative cathartic ability

Another significant representative of this period was Areteus from Cappadokia (second century A.D.). In his four preserved works, one can find many references to skin catharsis either through provocation or when the organism performs it on its own. In his book, *On Causes and Signs of Chronic Sufferings: Book II*, referring to dropsy, he wrote, "*Dropsy is bad for any illness. However, from these* (forms of dropsy) *phlegmasia alba dolens* (or milk-leg) *is the most benign. This happens because, as it fortunately occurs in most cases, sweat, urine or diarrheas coexist and dropsy is solved.*"

Furthermore, in the same book, a little further on he wrote, "*If in the case of dropsy, urine is much, dense and contains muddy materials, then there is some hope that dropsy will be solved. If, however, they are thin and few in quantity then this condition maintains the dropsy. If the disease changes course, as to its original form, and turns to the abdomen then by causing many and viscous watery evacuations the dropsy will be treated. Nevertheless, this therapy carries some risk due to the fact that many evacuations lead finally in the patient's exhaustion or hemorrhage and death due to weakness. It is not dangerous if sweat solves* (the dropsy), *only when it is excreted in significant quantities. Because these* (patients) *do not sweat a lot*" [29].

Ruphus' "chronic renal failure"

Within this period, Ruphus from Efessus, whom the Byzantine doctor Oribasius called "a Great physician," appeared and prospered. Ruphus made an important reference in the section "*on the sclerosis of kidneys*" where he seemed to give a description of chronic renal failure:

"*Whenever scleroses develop in the kidneys they are painless and, as someone would expect, the loins are hanging and the hips are restricted in their movements and the legs are weak; they discharge a small quantity of urine resembling greatly the conditions affecting patients with edemas. And these patients of course, in the course of time, are filled up with water as the other viscera become sclerosed, too*" [30].

In his works, Ruphus mentioned the same cathartic methods as the other physicians, namely venesection, enemas, diuretic drugs, embrocations, cupping, baths, and a careful diet. However, he added an interesting method for provoking perspiration in his work, *On the Renal and Cystic Diseases*, and in the paragraph on polyuria (urine diarrhea): "*. . . because it is good for them to be able to perspire if diuresis stops. The best of all is a steam bath in a small vat with the head coming out from the top, so that, while the rest of the body is being heated, one can breathe cool air.*"

Archigenis' nocturnal skin catharsis

A brief reference to catharsis through the skin also appeared in the few extant manuscripts by Archigenis, the physician who flourished in the emperor Trajan's time (end of first and beginning of second century A.D.). He observed:

"*Common is the treatment of all dropsical patients. Their bed should be very soft, and especially for those showing anasarca edema, we should lay reed leaves under it and other drying herbs, like osier* [agnus castus (or chaste tree)], *kalaminth and the such. It is indeed wondrous the way in which the edema disappears during sleep so that some of those who were covered under piles of wheat, got up withered after their sleep. The covers should be rougher and the house temperature temperate according to the season of the year*" [31].

Archigenis was probably the first physician in history who mentioned catharsis through the skin during sleep, something we try to achieve today by automated peritoneal dialysis during sleep.

EARLY BYZANTIUM: ORIBASIUS, AETIUS, ALEXANDER OF TRALLES, PAUL OF AEGINA (300 TO 700 A.D.)

Most physician writers of this period were involved in the study of ancient physicians. They repeated the theories and methods of the ancients, sometimes copying their texts exactly and other times combining various physicians' methods, analyzing them, and often paraphrasing older views in order to present them as their

own. Consequently, no rapid development in therapeutics occurred during this period.

Oribasius's sand baths

According to researchers of Byzantine medical history, this period began with Oribasius from Pergamene (fourth to fifth century A.D.), who emphasized, "*It is not useful to always cause perspiration in somebody who is bathing. Because we often take to a bath not to empty the body, but to moisten it all when very dry*" [32].

The skin's amphidromic permeability was obviously familiar to Oribasius. The therapeutic methodology's objective did not change in Oribasius' texts compared with more ancient writers. The body's cathartic insufficiency constituted a significant cause of sickness, resulting in the accumulation of harmful substances. Chapter 8 of his tenth book was dedicated to the therapeutic use of sand baths. One of the indications, among others, was edema:

"*Heating through the sand is appropriate for asthmatic patients and those who have rheumatic diseases in the chest and abdominal diseases and gout and paralyzes and cachexia and edemas and any chronic painful illness. Suitable for therapy are all patients except for very young children.*"

Oribasius described this method in detail beginning from the way the sand was prepared: "*You should therefore dig two or three deep holes of equal size at dawn and let them become overheated from the sun*," moving on to the positioning of the patient, depending on the illness, and extra care like covering the head so it didn't get burned from the sun's rays or the administration of fresh water if necessary. "*As for the dropsical patients, the number of days that it* (a sand bath) *takes place should be proportional to the volume that must be removed. The benefit from this you should examine 21 days later and after a break of two or three days you should start again*" [33].

The detailed description showed that the method was widely spread, and the instructions were derived from experience and observation, and not from untried theories.

The time after Oribasius was rather poor in physician writers until the sixth century A.D. when two great personalities excelled in medicine. The first was Aetius Amidinus, and the second was Alexander from Tralles. Aetius wrote 16 books in which therapeutics dominated, combined with very few elements of anatomy and pathophysiology. Although they did not differ essentially from the writings by Orivasios and his predecessors, at certain points, he provided more information on his views.

Aetius's contribution to therapeutics

In his third book and in the chapter on sand baths, Aetius mentioned that the objective of a sand bath as well as other methods of body heating was no other than the increase of insensible transpiration and perspiration: "*the insensible transpiration it intensifies and the sweat it extracts.*"

The benefit of this increase of insensible transpiration and perspiration was evident "*in dropsical and nephritic patients . . . and those who have developed a chronic disease of the cyst.*"

In Aetius' work, phlebotomies were also mentioned, as well as thermal baths and cupping, and all other methods for catharsis referred to by previous physicians. Aetius also repeated his predecessor Archigenis's opinion on the use of baths to provoke perspiration [34]. In the chapter "*On Edemas*," he rendered his own pathophysiological interpretation and therapeutics for edemas, which were described in detail as edemas that leave a recess after exercising pressure and which should be treated with increased perspiration [35].

Alexander's physical examination, diagnosis and treatment

A generation after Aetius another famous physician appeared in Asia Minor, Alexander from Tralles of Lydia, (525 to 605 A.D.). He identified ascites from the "*lurching as happens with a skinbag when one stirs the fluid that it contains*," tympanites that "*when we beat it a sound is produced as occurs with a drum beating*," and anasarca edema from "*the swelling of the entire body which when it is pressed with a finger a concavity is formed and when we stop pressing it the concavity does not immediately assume its previous form.*"

Alexander's observations have great importance since he provided different treatments for each diagnosis, thus showing an understanding of the existence of different pathophysiological mechanisms. If a proper diagnosis was made, then "*we treat ascites and tympanites with purgatives, whereas for the anasarca edema, we also employ venesection if it is needed*" [36].

Paul's therapeutic "safety rules"

The earlier Byzantine age ended with Paul of Aegina (625 to 690 A.D.), who lived most of his life in Alexandria, Egypt. His auctorial work, *Epitome*, contained pharmaceutical and other treatments that in most cases were a mere copy of precedent authors' views. Paul knew very well the consequences of a sudden loss of fluids and provided clear instructions with respect to the quantity that should be eliminated. In his description of abdominal catheterization for the relief of ascites,

"*Anyone interested in ensuring the patient's safety must remove a small amount of fluid with the operation so that the patient is relieved of the force exerted by his excessive weight, and as for the remaining fluid this is eliminated with the use of medication that helps the body eliminate liquids, with sand-baths and sun-therapy as well as by*

recommending him to abstain from drinking liquid and by eating dry food."

The fluids that were accumulated in the suffering body could be eliminated either surgically as in the case of ascites or with classic methods such as sand bathing and enemas, or by combining both as it occured with cut cupping because, "*not only blood comes out but fluids, too. And if it is necessary to remove a small quantity of liquids then a few or even one incision is enough; if however, the fluids are many then many incisions are also required*" [37].

MIDDLE BYZANTINE AGE: STEFANUS FROM ALEXANDRIA, MELETIUS THE MONK (SEVENTH TO ELEVENTH CENTURY A.D.)

After the seventh century A.D., Byzantium gradually lost its philosophical and scientific prestige. There were minor references in the works of a few scholars such as those of Stefanus from Alexandria and Meletius the Monk.

Stephanus's thoughts on the nature of perspiration

Stefanus from Alexandria lived in Constantinople in the 7th century A.D. and taught in the university established by the Byzantine emperor Theodosius II. Very likely, Stefanus did not practice medicine himself; however he wrote many treatises, "memorandums" on Hippocrate's, Galen's, and Aristotle's works, as well as various works on philosophy and astronomy. In his treatise on Hippocrate's *Prognosticon*, he referred to the causes that produce perspiration. He also took up Erasistratus' ideas inasmuch as he wrote:

"*The organ that produces sweat is the pores through which this sweat comes. And the raw material is all liquids, that is all juices that are in excess; this is proved by the color, the taste and the smell of perspiration in the baths as well as on the clothes of men who sweat, which have various colorings . . . various tastes . . . and various odors as they are generated by different fluids*" [38].

Moreover, in his work *Elaboration on Galen's Therapeutics Dedicated to Glaphkon*, he described baths and their uses [39].

Meletius' physiology of digestion and perspiration and his microcosmos–macrocosmos perception

Meletius the Monk, who lived approximately 850 A.D., was a conscientious compiler of famous ancient and Christian authors, as he himself clearly stated. In his reference on the physiology of digestion, he repeated Galen's views and spoke of three kinds of digestion: that which occurred in the stomach, that of the liver, and finally, that of the rest of the body. In his "*Essay on the Nature of Man*," he wrote:

"*The waste matter of the third digestion is derived from the entire body and is called perspiration. It is purified through insensible pores. And all that takes place so, that this waste is not accumulated in the course of time and becomes decomposed into the intestines thus producing harm to the animal*" [40].

In chapter 12 entitled "*On the Skin and Hairs*," he wrote with respect to the usefulness of skin, "*It eliminates from the body all that is redundant and for this reason it is entirely covered with holes so that respiration and sweat excretion are made possible.*"

He continued to perpetuate the age-old idea of the similitude between the microcosm and the macrocosm [41] when he wrote, "*The creative or better yet, guardian nature . . . in caring for the animal, it created channeling pores through which the waste and muddy substances of the body are purified. Because as it knew that food is on one hand useful to the body but also has wasteful elements, for this reason it invented these* (pores) *just as they, who care for cities, build sewers and streams, so that whatever waste matter is collected it can be eliminated into lakes, rivers or seas.*"

LATER BYZANTINE: NICEPHORUS VLEMMYDES, NIKOLAUS MYREPSUS, IOANNIS AKTUARIUS (TWELTH TO FIFTEENTH CENTURY A.D.)

In this period, Nicephorus Vlemmydes, Nikolaus Myrepsus, and Ioannis Aktuarius were distinguished physicians. One report on the medicine of this period was found in the poem "*On Urines*" by Nicephorus Vlemmydes, in which the methods for dealing with the disease did not change: enemas, baths, and embrocations [42]. Nikolaus Myrepsus demonstrated a method of spa therapy for very fat people, observing that a few days of increased perspiration, they thin and grew so much slimmer that "*neither they who see them with their own eyes believe it*" [43]. He, thus, calls to mind current advertisements of slimming centers, where by means of diuretics, massage, and saunas, they also promise tremendous weight loss. Ioannis Aktuarius, an eminent Byzantine doctor who lived during the fourteenth century, referred to the four digestions in his work, *On Urines by the Wisest Aktuarius.* The third digestion's waste product was urine, and the fourth, which was the conversion of blood into flesh, produced a substance that was eliminated through the skin by insensible transpiration [44].

In his many works, there were also references to various methods of catharsis. In a chapter of his treatise on dropsical patients, Aktuarius described the following methods of treatment: diuretics, purgatives, enemas, emetics, perspiration, baths, scarifications, cataplasms, embrocations, and perforation of the abdominal cavity as Paul Aeginites described it.

By the era of Late Byzantium, medical knowledge

became more universal and not the exclusive asset of the Byzantines, the Arabs, and the Hebrews. The Latin West emerged from the Middle Ages to prepare for the early Renaissance.

THE SKIN AS AN EXCRETORY ORGAN

At this point, it is worth comparing some attributes between skin and kidneys. The blood supply of both kidneys ranges within 12 to 30% of the cardiac output, with the usual output being approximately 22% and is analogous to the skin's. The kidneys' ability to eliminate liquids rarely amounts a maximum of 10 L per day even in pathological cases of diabetes insipidus, while the skin can eliminate 12 L on a hot summer day [46]. Despite the fact that the average human skin surface is reported to be approximately 1.8 m^2, in reality, this is much greater inasmuch as the skin has numerous folds as it occurs for example for a human weighing 70 kilos and 1.70 cm tall [(surface in m^2) = weight in $kg^{0.425}$ × height in $cm^{0.725}$/ 139.315] [47]. It is also interesting to note that the surface of the peritoneum is also approximately 1.7 to 2 m^2 [48]. The excretory ability of the skin is not limited to water, potassium, sodium, and urea. Creatinine, calcium, phosphorus, histamine, prostaglandins, amino acids, lactic acid, pyruvic acid, glucose, drug substances, and heavy metals are some of the substances that are found in the analysis of human perspiration [49]. Actually, the only restrictive element regarding the capacity of the skin to excrete substances is the aggregation of these substances. Finally, it is worth mentioning the excretion of bicarbonates in the excretory spiral, and their almost complete reabsorption in the excretory pore so that eventually the perspiration becomes acid (pH 5 to 6.5). The skin has approximately 2.5 million sweat glands, while each human kidney has approximately 1.2 million nephrons. In other words, the total number of a human's nephrons amounts to the same number as that of the sweat glands. Both in the skin and the kidneys, as well as in many other tissues, the aquaporines seem to play the primary role for the elimination of water on a molecular level, as they are special protein channels on which the activity of the cellular membrane's permeability to water depends. The role of the skin as an excretory organ is also demonstrated by the fact that in the sweat glands as well as in the kidneys receptors exist for aldosterone and antidiuretic hormone (ADH) [50]. The eliminated quantities of water and carbon dioxide through the skin are minimal in contrast to those eliminated by the lungs; nevertheless, they must be important for life, as shown by the following experiment. Fowls were placed in firmly closed boxes with their head protruding outwards. Although their respiration from the lungs was thus not obstructed, they died after a period of time because of the fact that their insensible transpiration was obstructed [51]. It is impressive that in the Hellenistic age, fowls were also closed in cages in order to prove experimentally the existence of insensible transpiration. (We describe this experiment later on.) The discussed limitations to the skin's excretory capacity apply to humans and other mammals. In contrast, in organisms on a lower scale of evolution—such as the scyphozoans and similar creatures, which have a very thin cover for their bodies—the epidermis is their only respiratory organ since they entirely lack a respiratory system. In addition, the uricotelic animals such as reptiles eliminate large quantities of uric acid through their skin [52].

Table 1. Mean daily temperatures in central Greece in 1998

Month	Mean temperature	
	Degrees Fahrenheit	Degrees Celsius
January	55	12.7
February	57	13.8
March	60	15.5
April	68	20
May	77	25
June	86	30
July	92	33.3
August	92	33.3
September	84	28.8
October	75	23.8
November	66	18.8
December	58	14.4

THE CLINICAL APPROACH

To obtain an estimate of the validity of the antiquarian theory of the skin's cleaning capacity, in a retrospective study design, we reviewed the average values for blood urea, creatinine, and electrolytes of all the patients in our dialysis unit in Patras, located in southwestern Greece, as well as those of three other dialysis units in Athens. The estimations were carried out during the winter/summer seasons of 1997, 1998, and 1999, and included three winter terms (that is, January, February, and March) and three summer terms (that is, July, August, and September). During these periods, the mean changes of temperature within the Patras' and Athens' area are very high (Table 1), as usually occurs in the Mediterranean countries. The total number included 161 patients on RDT. We compared 934 pairs of values for the same patients between winter and summer. Their dietary intake was unchanged during the period of the study.

We found a significant difference of 16 mg/dL in the average blood urea between the winter and summer months (mean winter urea 182 mg/dL and mean summer urea 166 mg/dL; $P < 0005$). There was no significant difference in the patients' body weights between the winter and summer months [45].

Having reviewed the skin's excretory mechanisms, we

believe that the skin catharsis is a very attractive hypothesis to explain the seasonal variation findings on several grounds. First, a 10°C rise of the external temperature on the surface of the skin triples the sweating rate until the mechanism is saturated. Second, the mean temperatures between summer and winter in our country differ by 20°C. Third, the concentration of urea in human sweat is 1.5 to 2 times the blood urea concentration in both healthy humans and chronic renal failure patients. Finally, during summer days, the loss of water through the skin ranges from 1.5 to 2 L/24 hours.

Therefore, we strongly suggest that the main reason for these results is the increased perspiration during summer days. It may not be an impressive increase, but the fact remains that the skin acts in this way operating at its minimum thermo-regulating capacity.

CONCLUSIONS

The hypothesis that the skin undertakes the role of a secondary kidney in renal failure is a very old one. The vast written material that survives from the classical and Byzantine periods shows the Greeks' fascination with the concept and their goal to study it in detail. Its allotted role is augmented by an increase of the external temperature. We hope that our findings concerning a seasonal variation of the RDT patient's blood urea reasonably support this antique idea.

Epilogue

The fifteenth century, in which this first part of our article stops, was not chosen arbitrarily. The period is considered the turning point between the Middle Ages and the Renaissance. During the fifteenth century A.D., four major evolutionary changes occurred: The fall of Byzantium to the Ottoman Turks, the expulsion of the Arabs from Spain, the invention of typography, and the discovery of America. Each one of these changes had a major impact on the evolution of scientific and, of course, medical knowledge. The impact of this evolution on the understanding of the mechanisms and applications of skin's catharsis is presented in the second part of our study.

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